Pharmacoeconomic analysis of proton pump inhibitor therapy and interventions to control Helicobacter pylori infection

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PART I

Proton Pump Inhibitors

Chapter 2

Meta-analysis: Comparing the Efficacy of Proton Pump Inhibitors in Short-term Use

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Abstract

Background: Proton pump inhibitors (PPIs) have a prominent role in the management of acid related diseases. Controlling expenses on PPIs would yield great economical benefits for Dutch healthcare. The aim of this study was to investigate whether clinical differences in PPIs exist.

Methods: Medline, EMBASE and the Cochrane library were searched. Papers were identified in English, German, French or Dutch in which two or more PPIs were compared under the same clinical conditions, in gastroesophageal reflux disease, peptic ulcer disease or *Helicobacter pylori* eradication. The pooled relative risks were calculated using the Mantel-Haenszel method.

Results: Two significant differences were found in the PPIs compared. In gastroesophageal reflux disease esomeprazole 40 mg was superior to omeprazole 20 mg (RR 1.18; 95%CI: 1.14-1.23). In peptic ulcer disease pantoprazole 40 mg was superior to omeprazole 20 mg (RR 1.07; 95%CI: 1.02-1.13). In *Helicobacter pylori* eradication no significant differences were found.

Conclusions: Both significant differences found were in favour of the highest dose of PPI on a milligram basis. This indicates that the difference may be dose dependent and not proton pump inhibitor specific. Therefore, when prescribing PPIs, other arguments than clinical efficacy, such as those related to pharmacoeconomics, may be considered.

Introduction

Proton pump inhibitors (PPIs) have a prominent role in the management of acid-related diseases. They are the drugs of choice in gastroesophageal reflux disease (GERD), peptic ulcer disease, in combination with one or more antibiotics in the eradication of *Helicobacter pylori* and as a gastric protective agent when using non-steroidal anti-inflammatory drugs. Before the introduction of PPIs, histamine-2-receptor antagonists (H_2RAs) and antacids were used in acid-related disorders. PPIs have shown to be more effective than H_2RAs and antacids in controlling acid-related diseases [1,2].

In the Netherlands PPIs comprised 66% of the prescriptions and 83% of the drug-costs in the acid suppressor group in the year 2000, whereas H_2RAs were responsible for 32% of the prescriptions and 17% of the drug-costs in the same year [3]. In the year 2000, PPIs were responsible for almost 10% of the total drug costs in community pharmacy in the Netherlands [4]. This indicates that controlling the expenses on PPIs would yield great economical benefits for the Dutch healthcare system.

Choosing a PPI can be based on different considerations. The costs, side-effect profile and possible interactions are some of the considerations on which the choice of a PPI can be based. These considerations are important, yet only decisive when there is no difference in clinical efficacy of the PPIs used. In this study randomised controlled trials were analysed where two or more PPIs were compared in the short-term management (4 weeks) of GERD, peptic ulcer disease or the eradication of *Helicobacter pylori*.

Methods

Justification

Medline, EMBASE and the Cochrane library were searched for meta-analyses concerning the efficacy of PPIs in short term treatment. Several papers were found,

comparing one or more PPIs with H_2RAs, and also a recent paper comparing different PPIs with omeprazole 20 mg in the acute treatment of reflux oesophagitis [5]. None of the papers found compared all PPIs in all dosages in the short term treatment of GERD, peptic ulcer disease and/or *Helicobacter pylori* eradication. As we aim to comprise this full spectrum we believe that our endeavour in an additional meta-analysis is justified.

Study selection

Medline (1985-2002), EMBASE (1985-2002) and the Cochrane library (whole period) were searched using the following keywords: omeprazol(e), pantoprazol(e), lansoprazol(e), lanzoprazol(e), rabeprazol(e), esomeprazol(e), GERD, GORD, ulcer, *Helicobacter pylori*, reflux, with the language restrictions English, Dutch, German or French. Abstracts from (poster) presentations at symposia were not included in the search. The studies found were further selected using the following criteria:

- A study should present new and original work;
- A study should compare two or more PPIs, under the same clinical conditions (for example same severity of disease, same dosing scheme, etc);
- Only studies concerning GERD, peptic ulcer disease or *Helicobacter pylori* eradication were included, as these reflect the main areas for proton pump inhibitor prescription;
- The studies had to be randomised prospective trials;
- Efficacy evaluation for GERD and peptic ulcer disease should be performed after 4 weeks of treatment, other time periods of evaluation were excluded;
- The presence of GERD and peptic ulcer disease (post- and pre-treatment) should be determined endoscopically;
- The detection of *Helicobacter pylori* (post- and pre-treatment) should be by urea breath test or endoscopy;

- Duration of *Helicobacter pylori* therapy should be between 7-14 days, studies with other regimen durations were excluded;
- End-point in studies concerning *Helicobacter pylori* eradication should be the eradication of *Helicobacter pylori*, studies only concerning symptom improvement were excluded;
- Studies concerning specific patient groups such as the elderly, children or mentally disabled persons were excluded; and
- Studies of pharmacokinetics, pharmacodynamics or pH-measurement were excluded.

The application of these criteria resulted in a final selection of 41 studies [6-46]. Of these studies 16 considered GERD [6-21], 9 considered peptic ulcer disease [22-30] and 16 considered *Helicobacter pylori* eradication [31-46].

Data Extraction and statistical analyses

The information retrieved covered PPI used, numbers of individuals treated, disease treated and success rate. Success rate was defined as endoscopically determined cure for GERD and peptic ulcer disease or assessment of absence of *Helicobacter pylori* after eradication. For every study the relative risk (RR) of the PPIs compared was calculated. Two independent researchers (BAvH and RMK) did data extraction and analysis. In case of disagreement a third researcher was consulted (JRBJB).

Where possible, the results were pooled using the Mantel-Haenszel method [47,48]. In this method, the weight given to the studies is based only on the number of patients in the study.

Table 1. Randomised double-blind studies comparing the efficacy after 4 weeks of different proton pump inhibitors in gastroesophageal reflux disease

Study	dose	N	Success†	Failure	CI	RR	CI
[6]	P40	103	81	22	0.73	0.99	1.35
	O20	105	83	22			
[7]	P40	170	126	44	0.71	0.95	1.28
	O20	86	67	19			
[8]	P40	10	3	7	0.09	0.33	1.23
	O20	10	9	1			
[9]	P40	60	45	15	0.70	1.07	1.63
	O20	60	42	18			
Pooled results for P40/O20[6-9]					0.88	0.97	1.06
[8]	L30	10	2	8	0.05	0.22	1.03
	O20	10	9	1			
[10]	L30	300	186	114	0.89	1.10	1.35
	O20	304	172	132			
[11]	L30	421	335	86	0.86	1.00	1.16
	O20	431	343	88			
[12]	L30	113	71	42	0.70	0.96	1.34
	O20	112	73	39			
[13]	L30	58	47	11	0.73	1.09	1.64
	O20	62	46	16			
[14]	L30	30	21	9	0.57	1.05	1.94
	O20	30	20	10			
Pooled results for L30/O20[8,10-14]					0.96	1.02	1.08
[15]	R20	100	81	19	0.73	1.00	1.35
	O20	102	83	19			
[16]	R20	104	92	12	0.73	0.97	1.29
	O20	103	94	9			
Pooled results for R20/O20[15,16]					0.91	0.98	1.06
[17]	E40	654	496	158	1.03	1.17	1.33
	O20	650	421	229			
[18]	E40	1216	993	223	1.08	1.19	1.30
	O20	1209	831	378			
Pooled results for E40/O20[17,18]					1.14	1.18	1.23
[11]	L15	218	157	61	0.75	0.90	1.09
	O20	431	343	88			
[16]	R10	103	88	15	0.70	0.94	1.25
	O20	103	94	9			
[17]	E20	656	462	194	0.95	1.09	1.24
	O20	650	421	229			
[19]	P20	166	128	38	0.74	0.95	1.21
	O20	161	131	30			
[20]	L30	104	91	13	0.81	1.09	1.46
	O40	103	83	20			
[21]	L30	235	188	47	0.81	0.99	1.21
	P40	226	183	43			

† Success is endoscopically healed GERD, P= Pantoprazole, O= Omeprazole, L= Lansoprazole, R= Rabeprazole, E= Esomeprazole, CI= Confidence interval, RR= Relative Risk

Potential problems with meta-analysis

When conducting a meta-analysis there are potential problems and sources of bias. One of the main problems in meta-analysis is publication bias. Studies with unexpected or spectacular results are more likely to be published than studies with unattractive results. In this case publication bias is probably of little importance, as clinical efficacy of PPIs is an important subject for decision-makers and clinicians and trial results are generally well-known.

Another problem in meta- analysis is selection bias. Selection bias is introduced when not all of the published articles concerning the subject are selected. Through selection, key-publications can be missed and the pooled result can be flawed. In this case selection bias is a problem, because not all languages and only full-text articles were selected. The impact of this bias is not clear. In addition, there are obviously less studies concerning the newer drugs (rabeprazole and esomeprazole).

Results

When comparing the different PPIs in the treatment of GERD one statistically significant result in the pooled RR was found. After 4 weeks esomeprazole 40 mg was shown to be superior over omeprazole 20 mg in endoscopic healing (RR 1.18; 95%CI: 1.14-1.23). In all the other comparisons no significant differences were found. (TABLE 1)

When comparing the different PPIs in the treatment of peptic ulcer disease one significant difference was found in the pooled RR. After 4 weeks pantoprazole 40 mg was superior to omeprazole 20 mg in ulcer healing (RR 1.07; 95%CI: 1.02-1.13). All other comparison showed no significant difference. (TABLE 2)

In the 16 studies concerning *Helicobacter pylori* eradication no significant differences were found (TABLE 3).

Table 2. Randomized double-blind studies comparing the efficacy after 4 weeks of treatment of different proton pump inhibitors in ulcer healing

Study	dose	N	Success†	Failure	CI	RR	CI
[26]	P40	124	118	6	0.83	1.07	1.38
	O20	131	117	14			
[27]	P40	146	128	18	0.83	1.14	1.56
	O20	73	56	17			
[28]	P40	193	178	15	0.80	1.03	1.34
	O20	93	83	10			
Pooled results for P40/O20[26-28]					1.02	1.07	1.13
[23]	L30	73	66	7	0.73	1.04	1.46
	O20	71	62	9			
[24]	L30	57	51	6	0.72	1.07	1.60
	O20	54	45	9			
[25]	L30	128	125	3	0.78	1.01	1.30
	O20	121	117	4			
Pooled results for L30/O20[23-25]					0.98	1.03	1.08
[29]	R20	102	100	2	0.79	1.05	1.39
	O20	103	96	7			
[30]	R20	113	103	10	0.76	1.00	1.31
	O20	114	104	10			
Pooled results for R20/O20[29,30]					0.97	1.02	1.08
[22]	L30	164	154	10	0.73	0.96	1.27
	O40	79	77	2			

† Success is ulcer healing, P= Pantoprazole, O= Omeprazole, R= Rabeprazole, L= Lansoprazole, CI= Confidence interval, RR=Relative Risk

Table 3. Randomized double-blind studies comparing the efficacy of different proton pump inhibitors in *Helicobacter pylori* eradication in the same regimens

Study	dose	N	Success†	Failure	CI	RR	CI
[31]	L60AM*	56	41	15	0.58	0.86	1.29
	O40AM	66	56	10			
[32]	L60AC*	93	68	25	0.63	0.88	1.22
	O40AC*	90	75	15			
[33]	L60AC*	186	134	52	0.90	1.17	1.51
	O40AC	170	105	65			
[34]	L60AC*	74	62	12	0.69	0.98	1.39
	O40AC	75	64	11			
[35]	L60A**	23	9	14	0.47	1.17	2.96
	O40A**	27	9	18			
Pooled results for L60/O40[31-35]					0.95	1.05	1.15
[36]	L30N**	26	20	6	0.61	1.21	2.39
	O40N	22	14	8			
[37]	L30AC*	73	60	13	0.72	1.03	1.47
	O40AC	75	60	15			
Pooled results for L30/O40[36,37]					0.92	1.06	1.23

Table 3. Continued

[34]	R40AC*	72	63	9	0.74	1.04	1.48
	L60AC	74	62	12			
[38]	R40AC*	104	89	15	0.77	1.03	1.39
	L60AC	104	86	18			
		Pooled results for R40/L60[34,38]			0.95	1.04	1.13
[39]	R20A**	101	63	38	0.67	0.94	1.33
	O40A	98	65	33			
[40]	R20AC*	58	51	7	0.72	1.07	1.59
	O40AC*	57	47	10			
		Pooled results for R20/O40[39,40]			0.87	0.99	1.14
[34]	R40AC*	72	63	9	0.72	1.03	1.45
	O40AC	75	64	11			
[46]	R40AC*	78	65	9	0.73	1.02	1.43
	O40AC	86	70	11			
		Pooled results for R40/O40[34,46]			0.93	1.02	1.13
[41]	P40CM*	25	25	0	0.64	1.14	2.02
	O40CM*	25	22	3			
[42]	P40AC***	79	66	13	0.64	0.89	1.23
	O40AC	84	79	5			
		Pooled results for P40/O40[41,42]			0.86	0.94	1.03
[32]	P80AC*	95	73	22	0.67	0.92	1.27
	O40AC*	90	75	15			
[42]	P80AC***	80	75	5	0.73	1.00	1.37
	O40AC	84	79	5			
		Pooled results for P80/O40[32,42]			0.88	0.96	1.04
[43]	E40AC*	204	183	21	0.83	1.02	1.26
	O40AC	196	172	24			
[44]	E40AC*	214	184	30	0.80	0.98	1.20
	O40AC	219	192	27			
		Pooled results for E40/O40[43,44]			0.90	1.00	1.11
[37]	L30AC*	73	60	13	0.76	1.10	1.57
	O20AC	76	57	19			
[45]	L30A***	14	4	10	0.17	0.62	2.19
	P40A***	13	6	7			

† Success = no *Helicobacter pylori* present, * = 7 days therapy, ** = 14 days therapy, *** = 10 days therapy, A= Amoxicillin, C= Clarithromycin, CI= Confidence interval, E= Esomeprazole, L= Lansoprazole, M= Metronidazole, N= Norfloxacin, O= Omeprazole, P= Pantoprazole, R= Rabeprazole, RR= Relative Risk

Discussion

As shown in the individual analyses, esomeprazole 40 mg was found to be superior to omeprazole 20 mg in GERD healing in the pooled analysis. This superiority is not surprising, because esomeprazole is the enantiomer of

omeprazole, and the active compound is the achiral cyclic sulphenamide. Comparing 40 mg of esomeprazole with 20 mg of omeprazole would be more or less the same as comparing double the dose of omeprazole [49]. The advantage of chirally pure esomeprazole compared with omeprazole is a more predictive and linear kinetics. The impact of this advantage for clinical practice is not yet clear. In all other comparisons concerning GERD, no significant differences were found in the PPIs compared.

In ulcer healing, 40 mg of pantoprazole was shown to be superior to 20 mg of omeprazole. This shows that it is not necessary to double the dose of pantoprazole compared to omeprazole in order to obtain the same results. The other comparisons of PPIs did not yield significant differences.

In the eradication of *Helicobacter pylori* no significant differences were found between the PPIs used in the eradication regimes. In the eradication of *Helicobacter pylori* all PPIs have a beneficial effect and failure of the eradication is mainly due to antibiotic resistance [50]. Therefore, in clinical practice small differences in PPI efficacy are probably of limited importance, with antibiotic resistance presenting the major impact. In order to determine whether there are differences in PPIs used, large trials should be designed including a correction for the effect of antibiotic resistance and compliance.

As significant differences were found only in two pooled results in which a higher dose of PPI was used for comparison, the differences found are probably dose dependent and not proton pump inhibitor specific. As expected, most comparative studies compared the first available PPI, omeprazole, with another PPI. For a better comparison of all PPIs, randomized clinical trials are needed in which comparisons between three or more different PPIs are made.

In this study, no account was taken of the potential effects and differences of long term PPI use. However, studies comparing different PPIs over a longer period of time have not show significant differences in safety and efficacy between the PPIs studied [51-54].

No economic data were considered in this study. However when all PPIs are clinically equal, the drug of choice could be that which is least costly on a daily dose base. In the Netherlands prices of PPIs for one month based on the "defined daily dose" (DDD) [55] are € 41.76 for esomeprazole 20 mg, € 42.96 for lansoprazole 30 mg, € 43.96 for omeprazole 20 mg, € 42.06 for pantoprazole 40 mg and € 37.89 for rabeprazole 20 mg [56]. The costs for rabeprazole on a DDD-basis are almost 14% less than those for omeprazole. As omeprazole has a market share of approximately 90% in the Netherlands, switching to rabeprazole could save up to € 30 million in the Netherlands. These drug prices were taken before generic omeprazole was available on the Dutch market; the introduction of generic omeprazole may have already resulted in a saving of € 15 million [57]. In a recent review Krömer *et al*. [58] suggest that the optimal dose in acute peptic ulcer disease and moderate to severe GERD is 30-40 mg, for omeprazole, lansoprazole and pantoprazole, for rabeprazole and esomeprazole there was not enough information at that time to suggest an optimal dose. For esomeprazole it will probably be the same as for omeprazole, given the presence of the same active compound [49]. This suggests when using the prices of the optimal dose, widespread use of pantoprazole and lansoprazole as compared to omeprazole and esomeprazole may potentially achieve a cost reduction. The place of rabeprazole is unclear because of the lack of sufficient data.

One of the problems of choosing the least expensive proton pump inhibitor is that changing the medication usually is inconvenient for the patient and may result in a lower efficacy of treatment [59]. Therefore most economic benefits may be expected in patients who are starting treatment.

In conclusion, all PPIs appear to be clinically comparable and clinical choice may be based on other factors, such as pharmacoeconomical considerations.

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